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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/050,359	03/31/98	FOWLKES D	FOWLKES-4B

HM12/1129

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EXAMINER	
MCCARTHY III,T	
ART UNIT	**PAPER NUMBER**
1618	9

DATE MAILED: 11/29/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/050,359	Fowlkes et al.
Examiner	**Group Art Unit**
McCarthy, T.C.	1618

☒ Responsive to communication(s) filed on *Mar 31, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24* is/are pending in the application.

Of the above, claim(s) *1-20 and 24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *21-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1.

Claims 1-20 and 24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention – the restriction requirement having been satisfied in paper no. 6 without traverse. Claims 21-23 are presently being examined on their merits.

Drawings

2.

Please review the attached PTO form 948 for required drawing corrections

Information Disclosure Statement

3.

The information disclosure statement filed 10/19/98 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the references have not been reviewed by the examiner because copies were not provided.

Claim Rejections - 35 USC ' 101

4.

35 U.S.C. 101 reads as follows:

> *Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.*

Claims 41 and 46-49 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

According to the text of 35 U.S.C. 101, an invention must be useful. Our reviewing courts have applied the labels "specific utility" (or "practical utility") to refer to this aspect of the "useful invention" requirement of this statute. Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881, 883 (CCPA 1980). In Nelson, the court characterized "specific utility" (or "practical utility") as a shorthand way of attributing real-world value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public. Id. at 856.

The claimed combinatorial libraries are not supported by a specific asserted utility and do not, without further research and experimentation, provide an immediate benefit to the public. Rather, the claimed combinatorial libraries comprise a collection of compounds that (as a whole) have no known biological activity, but that are merely drug or ligand candidates. Instant specification, pages 25-36. Any benefit to the public is therefore speculative. There is no basis in the specification upon which to conclude that any specific compounds encompassed by the

library are, or will turn out to be biologically active after testing. Even if the test compounds show affinity for a target protein, this does not indicate that pharmacological activity must necessarily follow. Thus, the biomedical research contemplated by the applicants is to take place at some future time, only when the properties of the claimed compounds have been elucidated by a battery of experimental methods to which the specification alludes. Absent a disclosure of those properties, the asserted utility of biomedical research lacks specificity. Furthermore, because the claimed invention is not supported by a specific asserted utility for the reasons set forth above, credibility cannot be assessed.

Many research tools such as telescopes, gas chromatograph, etc., have clear, specific and unquestionable utilities. See USPTO Utility Guidelines, page 12. However, inventions that have a specifically identified utility must be distinguished from those whose utility requires further research to identify or confirm. See id. Research tools (such as gas chromatograph) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves. The claimed combinatorial libraries are not research tools in this sense. They are themselves the subject of basic research, whose usefulness or lack thereof has yet to be established. See id at page 44, example A.

In the absence of an asserted specific utility, the useful requirement may be established to a well established utility. A well established utility is a specific utility which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. The combinatorial libraries claimed are not supported by a well established utility because neither the specification as filed nor any art of record discloses or suggests any property or activities for the claimed compounds (i.e. X-R-X) such that another non-asserted utility would be established for the

compounds. Further, the compounds of the claimed libraries are not recognizable as analogous to compounds with a recognized pharmacological (or other) activity (X-R-X is not a recognizable peptide). In the absence of any data as to their activity, there is no basis upon which to base either a specific or well-established utility.

Claim Rejections - 35 USC § 112

5.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using moderately sized libraries, does not reasonably provide enablement for making and using libraries of any size. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to either make or use the invention commensurate in scope with these claims. For example, given only a single library, wherein (a) each peptide is 30 amino acids long, and (b) each residue is varied only within the twenty natural amino acids, one would arrive at a library of 20^{30} peptides. Assuming (a) the amino acids have a mean mass of 110 daltons and (b) that each peptide is present in 1 micromole quantities, this would translate into a panel 20 peptide libraries, the total mass of which would be on the order of 6×10^{10} Kg. Addition of a solid phase or production of

more than 1 micromole of peptide product will increase the total mass dramatically. The applicants have not disclosed how to make and use a panel of such libraries, whose combined mass could conceivably exceed even that listed above (Note: these are first-order calculations, and do not include the limitation of fixing one of the amino acids – applicants are urged to perform their own calculations to ensure that the examiner's are not in error). Applicant is therefore required to amend the claims such that one of ordinary skill in the art can make and use the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "middle 50%" in claim 21 is a relative term which renders the claim indefinite - especially when peptides comprising the libraries are composed of odd numbers. The applicant does not specify how one of skill in the art is to define the middle 50% of a peptide. Furthermore, the term is not defined in either the claims or the specification, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention (i.e. its metes and bounds) as the claim currently reads.

Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "having" in claim 21 is a relative term which renders the claim indefinite. The applicants do not disclose in their specification how "having" is to be interpreted. Furthermore, dependent claims 22 and 23 further limit and add elements to claim 21 – thus

demonstrating that "having" in the immediate case must be interpreted as open (see MPEP chapter 2100, section 2111.03). If the applicants intend for the descriptions of their libraries to use closed language, the claims must be amended.

Claim Rejections - 35 USC ' 102

6.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> *A person shall be entitled to a patent unless --*
>
> *(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

The following 102 rejection is based on the assumption that the term "having" in claim 21 is open – thus implying that the language of claims 22-23 is open as well. Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Pinilla et al. (1995). Pinilla et al. teach (in their table 1) several peptide libraries in which at least one amino acid is held constant while the other amino acids are varied among either (a) the 20 natural or (b) any nonnatural amino acids. Of particular interest are the positional scanning libraries wherein the fixed amino acid "O" is located within the middle 50% of the peptide. Inherent to these teachings are the formation of a panel of peptide libraries in which O is different from library to library, and in which all possible genetically encoded peptides of a predetermined length are represented. In other words, by varying "O" within any of the 20 available amino acids (or any nonnatural

amino acids) table 1 inherently teaches the creation of a panel of at least 20 biased peptide libraries, with at least one fixed amino acid in each library being in the middle 50% - and where the numbers of variable amino acids on either side do not differ by more than 2. This argument for inherency is enforced by Pinilla et al.'s statement on page 225: "It should also be noted that each positional SCL, while addressing a single position of the sequence, represents the same collection of individual peptides."

Furthermore, by varying the non-fixed amino acids, one will inherently arrive at all possible amino acid/peptide combinations disclosed by the applicants claims. In other words, the teachings of Pinilla et al.'s table 1 are equivalent to holding one amino acid fixed and scanning another fixed amino acid position throughout the library. If one were to create a panel of biased peptide libraries using the teachings of Pinilla et al. and then compared them to the biased "scanned" libraries of the applicant, both panels would be composed of the same peptides, because both result in the creation of all possible combinations. Therefore, the teachings of Pinilla et al. anticipate all of applicants claims 21-23.

7.

Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Huffman et al. (1995). Huffman et al. teach (in their page 14 lines 11-35) the creation of panels of libraries in which at least one amino acid is held constant – anywhere in the peptide (i.e. including the middle 50%) - while the other amino acids are varied. He also discusses the formation of positional scanning libraries wherein the fixed amino acid "O" is optimized, and then a second amino acid is varied to create panels. These library panels also will contain all of the peptides disclosed in the applicants claim 23.

8.

The following 102 rejection is based on the assumption that the term "having" in claim 21 is open – thus implying that the language of claims 22-23 is open as well. Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Pinilla et al. (1992). Pinilla et al. teach (in their upper right hand paragraph on page 901) the creation of panels of libraries in which at least one amino acid is held constant – anywhere in the peptide (i.e. including the middle 50%) - while the other amino acids are varied. This teaching also anticipates the applicants claims 21-23 for the reasons outlined in paragraph 6, above.

9.

Claim 23 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Spatola et al. (1996). Spatola et al. teach (in their table 1) the creation of panels of libraries in which Asp is held constant in the middle 50% of the peptide (the peptides are cyclic so it is in the middle 50% no matter where it is placed) while the position of Pro is varied (see their libraries L1, L13, L25, and L37).

10.

> *(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 3718 of this title before the invention thereof by the applicant for patent.*

Claims 21-22 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Cantley et al.'s column 10 line 41 to column 12 line 1.

Claim 23 is rejected under 35 U.S.C. 102(e) as being anticipated by Cantley et al.'s column 10 line 41 to column 12 line 1, because if one were to create a panel of biased peptide libraries using the teachings of Cantley et al. and then compared them to the biased "scanned" libraries of the applicant, both panels would be composed of the same peptides, because both result in the creation of all possible combinations. Therefore, the teachings of Pinilla et al. anticipate all of applicant's claims 21-23.

11.

The following 102 rejection is made based on the interpretation that the term "having" in claim 21 is open claim language. Claims 21-23 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Holmes' (US Patent 5,770,456) teaching in figure 7, wherein a panel of 36 biased combinatorial hexamer peptide libraries (of 20 peptides each) in which one amino acid is held constant ("A"), one position varied among the 20 amino acids, and a second fixed amino acid are varied systematically (i.e. "scanned")in terms of their positions in the peptide sequences. Because the library is cyclic, "A" is always in the middle 50% and the chain length on either side of "A" never varies by more than 2 amino acids.

Claim Rejections - 35 USC ' 103

12.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 23 is also rejected under 35 U.S.C. 103(a) as being unpatentable over Holmes (US Patent 5,770,456), when Holmes is taken as a whole.

Claim 23 is rejected for the following reasons:

Holmes teaches in figure 7 a panel of 36 biased combinatorial hexamer peptide libraries (of 20 peptides each) in which one amino acid is held constant ("A"), one position varied among the 20 amino acids, and 5 fixed amino acids are varied systematically (i.e. "scanned")in terms of their positions in the peptide sequences. Because the library is cyclic, "A" is always in the middle 50% and the chain length on either side of "A" never varies by more than 2 amino acids.

The claim differs because in figure 8 Holmes does not use 4 variable sites, one fixed amino acid at a constant position, and one fixed amino acid whose position is "scanned" with respect to the other fixed amino acid. However, it would have been prima facie obvious - for anyone skilled in the art at the time of invention - to modify the panel of Holmes' figure 8 such that its libraries did include the limitations of applicants' claim 23 when Holmes is taken as a whole.

One would have been motivated to make this substitution because Holmes teaches it in column 12 lines 61-65, and indicates elsewhere (i.e. throughout the entire document) that this systematic substitution method increases the speed/number of hits in a lead optimization process.

Also, Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinilla et al. (1995) in view of Huffman et al. (WO 95/01800).

Claim 21 is rejected for the following reasons:

Pinilla et al. teach in their table 1 several peptide libraries in which at least one amino acid is held constant while the other amino acids are varied among either (a) the 20 natural or (b) any nonnatural amino acids. Of particular interest are the positional scanning libraries wherein the fixed amino acid "O" is located within the middle 50% of the peptide. Inherent to these teachings are the formation of a panel of peptide libraries in which O is different from library to library, an in which all possible genetically encoded peptides of a predetermined length are represented. In other words, by varying "O" within any of the 20 available amino acids (or any nonnatural amino acids) table 1 inherently teaches the creation of a panel of at least 20 biased peptide libraries, with at least one fixed amino acid in each library being in the middle 50% - and where the numbers of variable amino acids on either side do not differ by more than 2. They also teach the variation of their libraries' peptide lengths to include peptides of virtually any size.

If the term "having" is intended by the applicants to be closed claim language, then claim 21 would differ because Pinilla et al.'s table 1 also teaches the formation of panels in which the fixed amino acid is located outside the middle 50% of the peptides. However, it would have been prima facie obvious - to one of ordinary skill in the art at the time of invention - to use only the panels in which the middle 50% of the library contains the first fixed amino acid when Pinilla et al. is taken in view of Huffman et al. (WO 95/01800).

One would have been motivated to make this addition because Huffman et al. teach in their lines 11-35 on page 14 that optimization of a panel of peptide libraries can be conducted by fixing the first amino acid at any location in the peptides – i.e. in the center (see their seq. I.D.

#7). He also teaches that variation in the method used to achieve convergence, but that they are all equivalent. Note that the peptides discussed by Huffman et al. in pages 14-15 are linear – not cyclic. One would have been motivated to combine these references because they are in the same technical field.

Claim 22 is properly included in the above rejection because none of the further limitations introduced by this claim overcome the above rejection.

Claim 22 is properly included because the variable amino acids on either side of Huffman et al.'s seq I.D. #7 do not vary by more than 2.

14.

In the event that the applicant's interpretation of a positional scanning library is different from the examiners' (see 102 rejections of claim 23, above), the following 103 rejection of claim 23 is also provided. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pinilla et al. (1995) in view of any one of Spatola et al. (1996), Lebl et al. (1995), or Holmes (US Patent 5,770,456).

Claim 23 is rejected for the following reasons:

Pinilla et al. teach in their table 1 several peptide libraries in which at least one amino acid is held constant while the other amino acids are varied among either (a) the 20 natural or (b) any nonnatural amino acids. Of particular interest are the positional scanning libraries wherein the fixed amino acid "O" is located within the middle 50% of the peptide. Inherent to these teachings are the formation of a panel of peptide libraries in which O is different from library to library, an in which all possible genetically encoded peptides of a predetermined length are represented. In other words, by varying "O" within any of the 20 available amino acids (or any

nonnatural amino acids) table 1 inherently teaches the creation of a panel of at least 20 biased peptide libraries, with at least one fixed amino acid in each library being in the middle 50% - and where the numbers of variable amino acids on either side do not differ by more than 2. They also teach the variation of their libraries' peptide lengths to include peptides of virtually any size.

In the case where one interprets that the claim differs because Pinilla et al. do not teach holding one amino acid fixed while scanning the position of another fixed amino acid, it would have been obvious to include a more explicit teaching of this method when Pinilla et al. is taken in view of Lebl et al.

One would have been motivated to make this addition because Lebl et al. teach in their section "Strategies for Optimization of the Primary Ligand" (page 192) that once two active subunits in a primary ligand have been identified, the space between these active subunits can be linked with a "variable length/variable composition linker library." Pinilla et al. teaches how to systematically identify two best amino acids for specific sites in a panel of biased libraries, and Lebl et al. teach that once two amino acids have been identified, the distance and compositions between them should be varied systimatically to even further optimize their ability to bind a target protein. One would have been motivated to combine these references because they are in the same technical field (in fact, they were found in the same issue of Biopolymers – separated by only one article).

Alternatively, it would have been prima facie obvious - for anyone skilled in the art at the time of invention - to modify the panel of Pinilla et al. such that their libraries included the limitations of applicants' claim 23 when Pinilla et al. is taken in view of Spatola et al. (1995).

One would have been motivated to make this substitution because Spatola et al. teach (in their left column of page 3843) the creation of panels of libraries in which a fixed amino acid is

held at a constant position while another fixed amino acid's position is varied systematically. In fact, Spatola et al. teach in this paragraph that this method is inherent to the method of Pinilla et al. (1995). They also explain how this method speeds the process of lead compound discovery. One would have been motivated to combine these references because they address the same technical problem: optimizing and/or discovering peptides that bind specifically to a target protein.

Alternatively, it would have been prima facie obvious - for anyone skilled in the art at the time of invention - to modify the panel of Pinilla et al. such that their libraries included the limitations of applicants' claim 23 when Pinilla et al. is taken in view of Holmes (US Patent 5,770,456).

One would have been motivated to make this substitution because Holmes teaches in figure 7 a panel of 36 biased combinatorial hexamer peptide libraries (of 20 peptides each) in which one amino acid is held constant ("A"), one position varied among the 20 amino acids, and 5 fixed amino acids are varied systematically (i.e. "scanned") in terms of their positions in the peptide sequences. Because the library is cyclic, "A" is always in the middle 50% and the chain length on either side of "A" never varies by more than 2 amino acids.

Claim 23 might still be interpreted to differ, however, because in figure 8 Holmes does not use 4 variable sites, one fixed amino acid at a constant position, and one fixed amino acid whose position is "scanned" with respect to the other fixed amino acid. However, it would have been prima facie obvious - for anyone skilled in the art at the time of invention - to modify the panel of Holmes such that its libraries did include the limitations of applicants' claim 23 when Holmes is taken as a whole.

One would have been motivated to make this substitution because Holmes teaches it in column 12 lines 61-65, and indicates elsewhere (i.e. throughout the entire document) that this systematic substitution method increases the speed/number of hits in a lead optimization process.

Conclusion

Applicant is also notified of some additional references (below), which are pertinent to the pending application, and which should optionally be reviewed in conjunction with the above arguments - especially if the applicant intends to amend claims 21-23. Some of the following references teach a variety of panels of libraries, with 1 or more fixed amino acids, and many provide motivation for including a preferred amino acid (i.e. proline) as the initial fixed residue.

Yu et al., Cell, vol. 76, 933-945, March 1994.

Kauvar et al. (any one of the following US Patents: 5,338,659; 5,851988; 5,846,722; 5,830,918; 5,674688; 5,717,085; 5,587,293; 5,340,474; 5,338,659).

Sparks et al., PNAS USA, vol. 93, 1540-1544.

Pinilla et al. (US Patent 5,556,762).

Searfoss et al. (US Patent 5,541,109).

Hornik et al. (US Patent 5,770,687).

Balint et al., Gene, vol. 137, 109-118, 1993.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T.C. McCarthy whose telephone number is (703) 308-5316. The examiner can normally be reached on Monday to Friday from 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams, can be reached on (703) 308-0570.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-7924.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

September 28, 1999

KEITH D. MacMILLAN
PRIMARY EXAMINER

T.C. McCarthy III, Ph.D.